Version with Markings to Show Changes Made

In the Specification:

The paragraph beginning at page 4, line 25, has been deleted and replaced with a new paragraph. The amendments are as follows:

Once an array has been prepared, the array may be exposed to a sample solution of target DNA or RNA molecules (410-413 in Figure 4) labeled with fluorophores, chemoluminescent compounds, or radioactive atoms 415-418. Labeled target DNA or RNA hybridizes through base pairing interactions to the complementary probe DNA, synthesized on the surface of the array. Figure 5 shows a number of such target molecules 502-504 hybridized to complementary probes 505-507, which are in turn bound to the surface of the array 402. Targets, such as labeled DNA molecules 508 and 509, that do not contains nucleotide sequences complementary to any of the probes bound to array surface do not hybridize to generate stable duplexes and, as a result, tend to remain in solution. The sample solution is then rinsed from the surface of the array, washing away any unbound labeled DNA molecules. Finally, as shown in Figure 6, the bound labeled DNA molecules are detected via optical or radiometric scanning. Optical scanning involves exciting labels of bound labeled DNA molecules with electromagnetic radiation of appropriate frequency and detecting fluorescent emissions from the labels, or detecting light emitted from chemoluminescent labels. When radioisotope labels are employed, radiometric scanning can be used to detect the signal emitted from the hybridized features. Additional types of signals are also possible, including electrical signals generated by electrical properties of bound target molecules, magnetic properties of bound target molecules, and other such physical properties of bound target molecules that can produce a detectable signal. Optical, radiometric, or other types of scanning produce an analog or digital representation of the array as shown in Figure 7, with features to which labeled target molecules are hybridized <u>702-706</u> [similar to 706] optically or digitally differentiated from those features to which no labeled DNA molecules are bound. In other words, the analog or digital representation of a scanned array displays positive signals for features to which labeled DNA molecules are hybridized and displays negative features to which no, or an undetectably small number of, labeled DNA molecules are bound.

Features displaying positive signals in the analog or digital representation indicate the presence of DNA molecules with complementary nucleotide sequences in the original sample solution. Moreover, the signal intensity produced by a feature is generally related to the amount of labeled DNA bound to the feature, in turn related to the concentration, in the sample to which the array was exposed, of labeled DNA complementary to the oligonucleotide within the feature.

The paragraph beginning at page 13, line 28, has been deleted and replaced with a new paragraph. The amendments are as follows:

While the polynucleotides of the double-stranded regions of an oligonucleotide linker must be internally complementary in order to produce the double-stranded body of an oligonucleotide linker, the sequences of single-stranded arms need to bear complementarity relationships with the sequences of single-stranded arms of one or more other oligonucleotide linkers. In Figure 14, the complementarity relationships are indicated by a graphical code, or markings, on the single-stranded arms of the oligonucleotide linkers. For example, the base sequence labeled **A** of the single-stranded arm <u>1414</u> [1404] of oligonucleotide linker 1402 is indicated by a single dark, central stripe 1420. A base sequence complementary to the base sequence **A** is designated as sequence **A'** 422 and is graphically indicated by reversing the colorations of the striped and non-striped portions of the graphical representation of the corresponding single-stranded arm. For example, dark colored stripe 1420 of sequence **A** is, in sequence **A'** 1422, a white-colored stripe 1424. In the following text, the labeled oligonucleotide linkers are referred to by the single-letter designators for their respective single-stranded arm sequences. Thus, primer oligonucleotide linker 1402 is referred to as linker **AB**, and oligonucleotide linkers 1403-1406 are referred to as **CDB'**, **CDA'**, **ABC'**, and **ABD'**, respectively. As shown graphically in Figure 14, sequence **A** is complementary to sequence **A'**, sequence **B** is complementary to **B'**, sequence **C** is complementary to **C'**, and sequence **D** is complementary to sequence **D'**. Note that all complementarity relationships are based on standard, anti-parallel, Watson-Crick hybridization.

The paragraph beginning at page 15, line 16, has been deleted and replaced with a new paragraph. The amendments are as follows:

Figure 18 illustrates addition of yet another layer of oligonucleotide linkers to the branching molecular complex covalently linked to the target/probe hybrid. The surface of the array, in Figure 18, is exposed to ligation solution III containing 20nM oligonucleotide linker **ABC'** 1804 (1405 in Figure 14), 20nM oligonucleotide linker **ABD'** 1802 (1406 in Figure 14), 30 mM Tris-HCl (pH 7.8), 10 mM $MgCl_2$, 10 mM dithiothreitol, 10 mM ATP, and 20 units of T4 DNA ligase. The **D'** and **C'** single-stranded arms of these two oligonucleotide linkers 1802 and 1804 hybridize with the **D** and **C** arms of the previously added oligonucleotide linkers to form a branching complex with eight unhybridized, single-stranded arms <u>1806-1813</u> [1806-1815]. Note that, in the described embodiment, each new addition of an oligonucleotide linker layer to the complex increases the signal-emitting entities bound to the target/probe hybrid by a factor of two, providing that the number of signal-emitting entities bound to, or incorporated within, the oligonucleotide linkers in each layer is identical. Thus, taking ligation of the primary oligonucleotide linker to the target/probe hybrid as shell zero, the concentration of signal-emitting chemical entities within the branching molecular complex is proportional to 2^n and the number of free, unhybridized single-stranded arms at the surface of the branching molecular structure is 2^{n+1}, where n is the number of shells. As in the previous addition of oligonucleotide linkers, the hybridized oligonucleotide linkers shown in Figure 18 are then covalently bound to the arms of the previously added oligonucleotide linkers via the DNA-ligase-mediated reaction. Figure 19 shows the branching molecular complex shown in Figure 18 following ligation.

The paragraph beginning at page 16, line 28, has been deleted and replaced with a new paragraph. The amendments are as follows:

Steps 2115-2129 form a control loop, or iterative inner process, in which layers of oligonucleotide linkers are added to the dendrimer-like molecular complex bound to target/probe hybrids. In step 2115, a loop-control variable "innershell" is set to Boolean value TRUE. In step 2117, the current value of the loop-control variable "innershell" is determined.

If the current value is TRUE, then a solution containing oligonucleotide linkers "CDB'" and "CDA'" (1403 and 1404 in Figure 14) is added to the surface of the array in step 2119. Otherwise, a solution containing oligonucleotide linkers "ABC'" and "ABD'" (1405 and 1406 in Figure 14) is added to the surface of the array in step 2121. Then, the added oligonucleotide linkers are covalently bound to the ends of the previously added oligonucleotide linkers in step 2123. In step 2125, the ligation mediator, cofactors, substrates, and buffering agents, as well as unhybridized oligonucleotide linkers, are washed from the surface of the array. In step 2127, the signal strength or calculated signal strength resulting from the current dendrimer-like branching complex is determined. If the signal strength is insufficient for analytical purposes, then, in step 2129, the loop-control variable "innershell" is assigned to the opposite value from its current value via a Boolean NOT operation, and control flows back to step 2117. Otherwise, sufficient signal generation and amplification has been carried out by techniques of the present invention, and the array may be analyzed in step 2131.